N->Q R57K (SEQ ID NO: 16), BACE N->Q R57del (SEQ ID NO: 18). The BACE N->Q construct contains 4 additional mutations of asparagines to glutamine and a C-terminal His tag as well as the arginine mutations. BACE N->Q without the His tag was mutated at 56 and 57 to give BACE N->Q R56K R57K no His (SEQ ID NO: 14).

Please delete the paragraph on page 25, lines 23-25, and replace it with the following paragraph:

SEQ ID NO: 19 is the activated from of SEQ ID NO: 6, SEQ ID NO: 21 the activated form of SEQ ID NO: 12 and SEQ ID NO: 20 the activated form of SEQ ID NO: 14, i.e. the form in which the protein is crystallized.

Please delete the paragraph on page 27, lines 7-14, and replace it with the following paragraph:

The crystal may be of the BACE protein of SEQ ID NO: 19 although as explained earlier any homologue, allelic form, species variant, derivative or mutein (as hereinbefore defined) may be used. Thus, it will be understood by those of skill in the art that some variation to the primary amino acid sequence may be made without significant alteration to the resulting crystal structure. Such minor variations include the replacement of one or more amino acids, for example from 1 to 30, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids by an equivalent or fewer number of amino acids.

Please delete the paragraph on page 27, lines 25, to page 28, line 7, and replace it with the following paragraph:

The methods described herein may be used to make a BACE protein crystal, particularly of a BACE protein of SEQ ID NOS 19-21, which method comprises growing a crystal by vapour diffusion using a reservoir buffer that contains 18-26 % PEG 5000 MME, preferably 20-24 % PEG 5000 MME, more preferably 20-22.5 % PEG 5000 MME, with 180-220 mM (e.g. 200 mM) ammonium iodide and 180-220 mM (e.g. 200 mM) tri-sodium citrate (pH 6.4-6.6). In a preferred embodiment, this reservoir buffer may also contain from 0 to 5% glycerol, e.g. about 2.5% glycerol. The growing of the crystal is by vapour diffusion and is performed by placing an aliquot of the protein solution on a cover slip as a hanging drop

above a well containing the reservoir buffer. The concentration of the protein solution used was approximately 7 mg/ml.

Please delete the paragraph on page 57, lines 6-16, and replace it with the following paragraph:

A cDNA construct encoding a modified BACE form was made as follows. A partial BACE cDNA fragment was amplified using the full-length BACE clone as a template with primers hBACE_EC(Bam-M-14)_FOR (5' - CGG GAT CCA TGG CGG GAG TGC TGC CTG CC - 3') **(SEQ ID NO: 43)** and hBACE_EC(Bam-453)_REV (5' - CGG GAT CCT TAT GAC TCA TCT GTC TGT GGA ATG TTG TAG C - 3') **(SEQ ID NO: 44)**. The resulting 1342 bp PCR fragment was subcloned in vector pCR2.1-TOPO using the TOPO TA cloning® kit (Invitrogen) according to the manufacturer's instructions. The inserts of several resulting clones were fully sequenced and a clone containing no PCR mistakes was selected. The insert of this clone was excised from the pCR2.1-TOPO construct using the *Bam*HI restriction endonuclease and subcloned to vector pET11a (Novagen) linearized with *Bam*HI. The BACE coding sequence (BACE WT, SEQ ID **NO:** 1) in the resulting clones was confirmed by sequence analysis and the resulting correct construct was named M-T7-RGSM(BACE14-453)/pET11a.

Please delete the paragraph on page 57, lines 18-22, and replace it with the following paragraph:

Plasmid M-T7-RGSM(BACE14-453)/pET11a encodes a 455 amino acid residue protein named BACE WT containing a T7 epitope tag encoded by the pET11a vector sequence (AA 1 to 11 **of SEQ ID NO: 2**), a linker sequence (AA 12-15 **of SEQ ID NO: 2**; RGSM) and the partial BACE amino acid sequence from residue 14 to 453 (AA 16 to 455)~~(numbering based on~~ **of** SEQ ID **NO:** 2). The calculated molecular mass of the resulting protein is 50.2 kDa.

Please delete the paragraph on page 57, line 23, to page 58, line 2, and replace it with the following paragraph:

The insert from construct Plasmid M-T7-RGSM(BACE14-453)/pET11a was amplified by PCR to incorporate a His$_6$ tag **(SEQ ID NO: 42)**(CAT CAC CAT CAT CAC CAC) **(SEQ ID NO: 45)** just upstream of the stop codon and *Bam*H1 site. Following cloning of this amplified fragment back into the original expression vector, the asparagine residues at positions -153, -172, -223 and –354 (numbers refer to the database BACE sequence BACE_HUMAN, P56817 in Swissprot) were mutated to glutamine (AAC to CAA) using the Quikchange™ mutagenesis system (Stratagene, used according to the manufacturers, instructions), to generate BACE N->Q (SEQ ID **NO:** 3).

Please delete the paragraph on page 58, line 11, to page 60, line 2, and replace it with the following paragraph:

Primers were applicable for the mutation of both BACE WT and BACE N->Q due to their high sequence homology. Seven constructs were produced; these are detailed below with the oligonucleotide sequence used to make the constructs.

1) BACE WT mutating arginine 56 to lysine and arginine 57 to lysine (SEQ ID **NO:** 5)

5' - CCCGAGGAGCCCGGCAAGAAGGGCAGCTTTGTGGAGATG – 3' (SEQ ID NO: 26)

5' - CATCTCCACAAAGCTGCCCTTCTTGCCGGGCTCCTCGGG – 3' (SEQ ID NO: 27)

2) BACE WT mutating arginine 57 to lysine (SEQ ID **NO:** 7)

5' – CCCGAGGAGCCCGGCCGGAAGGGCAGCTTTGTGGAGATGG – 3' (SEQ ID NO: 28)

5' – CCATCTCCACAAAGCTGCCCTTCCGGCCGGGCTCCTCGGG – 3' (SEQ ID NO: 29)

3) BACE WT deleting arginine 57 (SEQ ID **NO:** 9)

5' – CCCGAGGAGCCCGGCAGGGGCAGCTTTGTGGAGATGGTGGAC – 3' (SEQ ID NO: 30)

5' – GTCCACCATCTCCACAAAGCTGCCCCTGCCGGGCTCCTCGGG – 3' (SEQ ID NO: 31)

4) BACE N->Q mutating arginine 56 to lysine and arginine 57 to lysine (SEQ ID **NO:** 11)

5' - CCCGAGGAGCCCGGCAAGAAGGGCAGCTTTGTGGAGATG – 3' (SEQ ID NO: 32)

5' - CATCTCCACAAAGCTGCCCTTCTTGCCGGGCTCCTCGGG – 3' (SEQ ID NO: 33)

5) BACE N->Q mutating arginine 57 to lysine (SEQ ID **NO:** 15)

5' – CCCGAGGAGCCCGGCCGGAAGGGCAGCTTTGTGGAGATGG – 3' (SEQ ID NO: 34)

5' – CCATCTCCACAAAGCTGCCCTTCCGGCCGGGCTCCTCGGG – 3' (SEQ ID NO:35)

6) BACE N->Q deleting arginine 57 (SEQ ID NO: 17)

5' – CCCGAGGAGCCCGGCAGGGGCAGCTTTGTGGAGATGGTGGAC – 3' (SEQ ID NO: 36)

5' – GTCCACCATCTCCACAAAGCTGCCCCTGCCGGGCTCCTCGGG – 3' (SEQ ID NO: 37)

7) BACE N->Q mutating arginine 56 to lysine and arginine 57 to lysine and removing the C terminal poly histidine tag (SEQ ID NO: 13)

5' - CCCGAGGAGCCCGGCAAGAAGGGCAGCTTTGTGGAGATG – 3' (SEQ ID NO: 38)

5' - CATCTCCACAAAGCTGCCCTTCTTGCCGGGCTCCTCGGG – 3' (SEQ ID NO: 39)

5' – CCACAGACAGATGAGTCATGACACCATCATCACCACTAAG – 3' (SEQ ID NO: 40)

5' – CTTAGTGGTGATGATGGTGTCATGACTCATCTGTCTGTGG – 3' (SEQ ID NO: 41)

Please delete the paragraph on page 66, lines 13-26, and replace it with the following paragraph:

<u>MS Analysis of BACE WT R56KR57K (SEQ ID NO: 6)</u>

Full-length protein: MASMTGGQQMGRGSMAGVLPAHGT…**(residues 1-24 of SEQ ID NO: 6)**

Predicted mass of full-length protein: 50147

Cleavage position:

MASMTGGQQMGR ↓ GSMAGVLPAHGT…**(residues 1-24 of SEQ ID NO: 6)**

Predicted mass of BACE protein: 48911. This is the first intermediate fragment and is obtained very quickly and can be obtained as a stable fragment at lower enzyme concentration.

Cleavage position:

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLR ↓

LPRETDEEP…**(residues 1-53 of SEQ ID NO: 6)**

Predicted mass of BACE protein: 45781. This is the final fragment obtained in the conditions described above. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 45783. The fragment typically elutes as a single peak from the Mono Q 5.5.

Please delete the paragraph on page 67, lines 1-9, and replace it with the following paragraph:

<u>Mass Spec Analysis of BACE N->Q R56KR57K (SEQ ID NO: 12)</u>

Predicted mass of full-length protein: 50895

Cleavage position:

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLR ↓

LPRETDEEP...**(residues 1-53 of SEQ ID NO: 12)**   .

Predicted mass of BACE protein: 46660.65. This is the final fragment obtained in the conditions described above. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 46655. The fragment typically elutes as two peaks from the Mono Q 5.5, the first corresponding to the desired fragment.

        Please delete the paragraph on page 67, lines 10-26, and replace it with the following paragraph:

<u>Mass Spec Analysis of BACE N->Q R56KR57K no His (SEQ ID NO: 14)</u>

Predicted mass of full-length protein: 50072.73

Cleavage position: .

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLR ↓

LPRETDEEP...**(residues 1-53 of SEQ ID NO: 14)**

Predicted mass of BACE protein: 45837.80. This is the first intermediate fragment, ·
obtained rapidly between 30-60 minutes post activation and is suitable for crystallisation. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 45838.30. Typically elutes as 2 peaks from the Mono Q 5.5, the first peak corresponding to the desired fragment.

Cleavage position:

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGK
↓ KGSFVEMV...**(residues 1-53 of SEQ ID NO: 14)**

Predicted fragment mass: 44230.11. Further digestion beyond 60 minutes promotes the formation of the above fragment, not suitable for crystallisation. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 44228.03. This typically elutes as peak 2 from the Mono Q 5.5.

        Please delete the paragraph on page 68, lines 2-7, and replace it with the following paragraph:

A fluorimetric assay was used to measure the activity of the refolded proteins. Activity of the BACE enzyme was measured using the fluorescent peptide R-E(EDANS)-E-V-N-L-*D-

A-E-F-K(DABCYL)-R-OH **(SEQ ID NO: 46)**(Bachem) as substrate. Assays were carried out in 96-well black, flat-bottomed Cliniplates in a final assay volume of 100ul. The reaction rate was monitored at room temperature on a Fluoroskan Ascent plate reader with excitation and emission wavelengths of 355nm and 530nm respectively.

Please delete the paragraph on page 76, lines 19-21, and replace it with the following paragraph:

11. A mutant BACE protein selected from: (a) SEQ ID **NO:** 6; (b) SEQ ID **NO:** 8; (c) SEQ ID **NO:** 10; (d) SEQ ID **NO:** 12; (e) SEQ ID **NO:** 14; (f) SEQ ID **NO:** 16; (g) SEQ ID **NO:** 18; (h) SEQ ID **NO:** 19; (i) SEQ ID **NO:** 20; (j) SEQ ID **NO:** 21.

Please delete the paragraph on page 81, lines 1-2, and replace it with the following paragraph:

54. The crystal of paragraph 43 wherein the BACE mutant is selected from: (a) SEQ ID **NO:** 19; (b) SEQ ID **NO:** 20; (c) SEQ ID **NO:** 21.

Please delete the paragraph on page 133, lines 1-24, and replace it with the following paragraph:

Sequence Listings

SEQ ID **NO:** 1: shows the DNA sequence coding for the BACE protein, BACE WT.

```
ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAGGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
```

```
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA
```

Please delete the paragraph on page 133, lines 25-32, and replace it with the following paragraph:

```
SEQ ID NO: 2: shows the deduced amino acid sequence for BACE WT.
MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRRGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES
```

Please delete the paragraph beginning on page 133, lines 33-48 and ending on page 134, line 9, and replace it with the following paragraph:

SEQ ID **NO:** 3: shows the DNA sequence coding for the BACE protein, BACE N->Q.

```
ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAGGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCAC
CACTAA
```

Please delete the paragraph on page 134, lines 10-17, and replace it with the following paragraph:

SEQ ID **NO:** 4: shows the deduced amino acid sequence for BACE N->Q.

```
MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRRGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDESHHHHHH
```

Please delete the paragraph on page 134, lines 18-41, and replace it with the following paragraph:

SEQ ID **NO:** 5: shows the DNA sequence coding for the BACE WT R56KR57K.

```
ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAAGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
```

```
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA
```

Please delete the paragraph on page 134, lines 42-49, and replace it with the following paragraph:

```
SEQ ID NO: 6: shows the deduced amino acid sequence for BACE WT R56KR57K

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGKKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES
```

Please delete the paragraph on page 135, lines 1-24, and replace it with the following paragraph:

```
SEQ ID NO: 7: shows the DNA sequence coding for the BACE WT R57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA
```

Please delete the paragraph on page 135, lines 25-32, and replace it with the following paragraph:

SEQ ID NO: 8: shows the deduced amino acid sequence for BACE WT R57K.

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES

Please delete the paragraph beginning on page 135, line 33 and ending on page 136, line 5, and replace it with the following paragraph:

SEQ ID NO: 9: shows the DNA sequence coding for the BACE WT R57DEL.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAGGGGCAGC
TTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATG
ACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTTT
GCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGC
ACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAAGGG
GAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCCAAC
ATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGCATC
CTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGAC
TCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCTGGC
TTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGAGGT
ATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGGTAT
TATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGCAAG
GAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCCAAG
AAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCT
GATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGGAAC
ATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGCATC
ACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGACGAC
TGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATG
GAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGCGCT
TGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTGGAC
ATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA

Please delete the paragraph on page 136, lines 6-13, and replace it with the following paragraph:

SEQ ID NO: 10: shows the deduced amino acid sequence for BACE WT R57del.

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRGSFVEMVDNLRGKSGQ
GYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLVS
IPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGFP
LNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNL
RLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLRP

VEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDES

Please delete the paragraph on page 136, lines 14-38, and replace it with the following paragraph:

SEQ ID **NO:** 11: shows the DNA sequence coding for the BACE N->Q R56KR57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAAGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCAC
CACTAA

Please delete the paragraph on page 136, lines 39-46, and replace it with the following paragraph:

SEQ ID **NO:** 12: shows the deduced amino acid sequence for BACE N->Q
R56KR57K

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGKKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDESHHHHHH

Please delete the paragraph beginning on page 136, line 47 and ending on page 137, line 22, and replace it with the following paragraph:

SEQ ID **NO:** 13: shows the DNA sequence coding for the BACE N->Q R56KR57K no
His.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAAGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC

```
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAG
```

Please delete the paragraph on page 137, lines 23-30, and replace it with the following paragraph:

```
SEQ ID NO: 14: shows the deduced amino acid sequence for BACE N->Q
R56KR57K no His

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGKKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES
```

Please delete the paragraph beginning on page 137, line 31 and ending on page 138, line 1 and replace it with the following paragraph:

```
SEQ ID NO: 15: shows the DNA sequence coding for the BACE N->Q R57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
```

```
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCAC
CACTAA
```

Please delete the paragraph on page 138, lines 2-9, and replace it with the
following paragraph:

SEQ ID NO: 16: shows the deduced amino acid sequence for BACE N->Q R57K

```
MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDESHHHHHH
```

Please delete the paragraph on page 138, lines 10-29, and replace it with the
following paragraph:

SEQ ID NO: 17: shows the DNA sequence coding for the BACE N->Q R57DEL.

```
ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCTGCCCACGGCACCCA
GCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGAGACCG
ACGAAGAGCCCGAGGAGCCCGGCAGGGGCAGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAG
GGCTACTACGTGGAGATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAA
CTTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGCACATACCGGG
ACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAAGGGGAGCTGGGCACCGACCTGGTAAGC
ATCCCCCATGGCCCCCAGGTCACTGTGCGTGCCAACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCA
GGGCTCCAACTGGGAAGGCATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTT
TCTTTGACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCTGGCTTCCCC
CTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGAGGTATCGACCACTCGCTGTACAC
AGGCAGTCTCTGGTATACACCCCATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCGGGTGGAGATCAATG
GACAGGATCTGAAAATGGACTGCAAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTT
CGTTTGCCCAAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCTGA
TGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGGAACATTTTCCCAGTCATCT
CACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGCATCACCATCCTTCCGCAGCAATACCTGCGGCCA
GTGGAAGATGTGGCCACGTCCCAAGACGACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTAT
GGGAGCTGTTATCATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGCG
CTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTGGACATGGAAGACTGT
GGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCACCACTAA
```

Please delete the paragraph on page 138, lines 30-37, and replace it with the
following paragraph:

SEQ ID NO: 18: shows the deduced amino acid sequence for BACE N->Q R57del

```
MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRGSFVEMVDNLRGKSGQ
GYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLVS
IPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGFP
LQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNL
RLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLRP
VEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDESHHHHHH
```

Please delete the paragraph on page 138, lines 38-44, and replace it with the following paragraph:

SEQ ID NO: 19: shows the amino acid sequence of BACE WT R56KR57K crystallised.

```
LPRETDEEPEEPGKKGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQ
LSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARP
DDSLEPFFDSLVKQTHVPNLFSLQLCGAGFPLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVII
VRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPW
NIFPVISLYLMGEVTNQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKR
IGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDES
```

Please delete the paragraph on page 139, lines 1-8, and replace it with the following paragraph:

SEQ ID NO: 20: shows the amino acid sequence of BACE N->Q R56KR57K no His as crystallised.

```
LPRETDEEPEEPGKKGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQ
LSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARP
DDSLEPFFDSLVKQTHVPNLFSLQLCGAGFPLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVII
VRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPW
NIFPVISLYLMGEVTQQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKR
IGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDES
```

Please delete the paragraph on page 139, lines 9-15, and replace it with the following paragraph:

SEQ ID NO: 21: shows the amino acid sequence of BACE N->Q R56KR57K crystallised.

```
LPRETDEEPEEPGKKGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQ
LSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARP
DDSLEPFFDSLVKQTHVPNLFSLQLCGAGFPLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVII
VRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPW
NIFPVISLYLMGEVTQQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKR
IGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDESHHHHHH
```